



Europäisches
Patentamt
European
Patent Office
Office européen
des brevets

Reply Due
By 4-21-08

European Patent Office
Postbus 5818
2280 HV Rijswijk
NETHERLANDS
Tel: +31 70 340 2040
Fax: +31 70 340 3016

PAT. REG. COMM.

DOCKET

ATTORNEY

MAINTENANCE

CASE REFERENCE

OTHER

Formalities Officer

Name: Ambrosch, Jens
Tel: +31 70 340 - 4259
or call
+31 (0)70 340 45 00

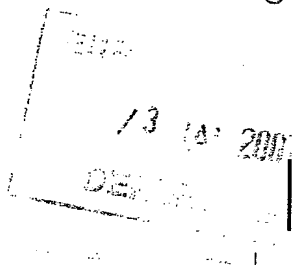
Substantive Examiner

Name: Bonzano, Camilla
Tel: +31 70 340 - 2202

PATENT DEPARTMENT

JAN 23 2008

Man, Jocelyn
Merck & Co., Inc.
European Patent Department [DARO]
Merck Sharp & Dohme Limited,
Hertford Road,
Hoddesdon
Hertfordshire, EN11 9BU
ROYAUME-UNI



Application No.
04 814 367.1 - 1216

Ref.

21592Y EPC

Date

21.12.2007

Applicant
Merck & Co., Inc.

Communication pursuant to Article 94(3) EPC

RECEIVED
11/23/08
(125)

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC.

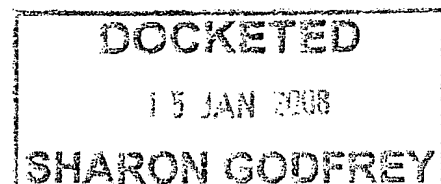
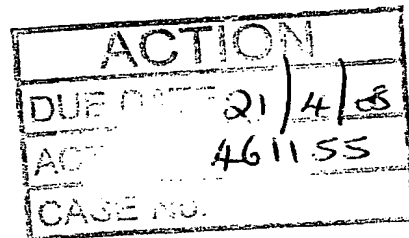
One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).



Bonzano, Camilla
Primary Examiner
for the Examining Division

Enclosure(s): 5 page/s reasons (Form 2906)



The examination is being carried out on the **following application documents**:

Description, Pages

1-85 as originally filed

Claims, Numbers

1-19 filed with entry into the regional phase before the EPO

Received

JAN 23 2008

Case Reference
Clerk

1. The following documents are being referred to:

- 20.01 D1: WO 2004/050619 A (GLAXO) 17 June 2004 (2004-06-17)
- 19.01 D2: WO 2004/080376 A (GLAXO) 23 September 2004 (2004-09-23)
- 18.01 D3: WO 03/045903 A (SMITHKLINE BEECHAM) 5 June 2003 (2003-06-05)
- 1.02 D4: WO 02 02512 A2

Article 123(2) EPC

2. The amendments filed upon entry into the European phase fulfil the requirements of Article 123(2) EPC.

Priority

3. The priority of the present application is only partially valid.

Claim 1 of the present application differs from the priority document in the following groups of the formula I: Q2, Q3 (which are always hydrogen in the priority document), Rb (3) and (6), R7 (c), R4-R7 (b) and R17 (g), which have all been added with respect to the priority document.

The same applies to present claims 12-14, which have, in the priority document, always Q2, Q3 being hydrogen.

Novelty (Article 54 (3) EPC)

4. The present application is not novel.

The provisions of Article 54(3) EPC 1973 apply to the present application, because it has a filing date earlier than 13.12.2007 (see Implementation of the decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the

Act Revising the European Patent Convention of 29 November 2000, Special edition No. 1 OJ EPO 2007, 197).

4.1 Document WO2004050619 (D1), from a different applicant, was published on the 17.6.2004, which is after the (partially valid) priority date of the present application, and has a filing date of 3.12.2003, which is earlier than the priority date of the present application. It is therefore an earlier application with respect to the present application.

It has been supplied to the European Patent Office in one of its official languages and the national fee provided for in Article 22, paragraph 1 or Article 39, paragraph 1 of the Co-operation Treaty has been paid. The requirements of Article 158(2) EPC 1973 are thus fulfilled.

D1 was granted.

D1 discloses compounds having a formula falling under the presently claimed formula: see claim 1 and in particular the following compounds (in pages 152, 153, 156, 160, 161, 167, 168, 170, 171 of the description).

E245, having R1=phenyl, m=1, Q1=OH, RA=dimethylhexylamino (Re being alkyl), R3=ethylamino, R2=dioxo isothiazolidin-2-yl (as in page 91, group (a) of substituents (1) of R2).

E246, with R3=isopropyl amino.

E250, having R3=ethyl amino.

E288, having R1=phenyl, m=1, Q1=OH, RA=dimethylhexyl amino (Re being alkyl), R3=ethylamino, R2=dioxo thiazinan-2-yl (as in page 91, group (b) of substituents (1) of R2).

E337, having R1=phenyl, m=1, Q1=OH, RA=methylbutylamino (Re being alkyl), R3=ethylamino, R2=dioxo tetrahydro thiazin-2-yl (as in page 91, group (b) of substituents (1) of R2).

E338-E343, having Ra= propylbutylamino, methylpentylamino, dimethylpentyl amino, methylbutylamino, propylamino, ethylamino respectively.

E345-E348, having Ra= methylpentyl amino, 5-methylhexyl amino, methylpropyl amino, 1-methylhexyl amino, respectively.

E431, having R1=phenyl, m=1, Q1=OH, Ra=butylamino (Re being alkyl), R3=ethylamino, R2=1,1-dioxotetrahydro-1,2-thiazin-2-yl (as in page 91, group (b) of substituents (1) of R2).

E439, E440, both having R1=phenyl, m=1, Q1=OH, Ra=trimethylpropylamino (Re being alkyl), R3=ethylamino, R2=1,1-dioxo 1,2-thiazinan-2-yl (as in page 91, group (b) of substituents (1) of R2).

E442-E445, E448, E449, having Ra=pentyl amino, hexyl amino, 3,3-dimethylbutyl amino, 1,1-dimethylpropylamino, ethyl amino, methyl amino, respectively.

E472, having R1=3-chloro phenyl, m=1, Q1=OH, Ra=dimethylhetylamino (Re being alkyl), R3=ethylamino, R2=1,1-dioxo 1,2-thiazinan-2-yl (as in page 91, group (b) of substituents (1) of R2).

E479, having R1= 2-furyl, m=1, Q1=OH, Ra=dimethylhexyl amino (Re being alkyl), R3=ethylamino, R2=1,1-dioxo 1,2-thiazinan-2-yl (as in page 91, group (b) of substituents (1) of R2).

All these compounds are described as being inhibitors of beta secretase, useful in therapy for treating Alzheimer's disease and other disorders characterised by elevated amyloid levels.

E279 has R1= phenyl, m=1, Q1=OH, Ra=cyclopropyl amino (Re being cyclo alkyl, instead of alkyl), R3=CONPr2 (R13,R14=propyl), R2=1,1-dioxo 1,2-thiazinan-2-yl (as in page 91, group (b) of substituents (1) of R2). This compound is different, but similar to the compounds of formula (I).

The subject matter of present claims 1,4,5,10,11,13,14,16-19 is therefore not novel in view of D1, as far as the same contracting states are designated (Article 54(3) EPC).

The compounds of claim 15 seem to be novel (in particular all those with the central pyridine ring).

4.2 D2 discloses different compounds for treating Alzheimer's disease. Being prior art under Article 54(3) EPC, it is not relevant, as far as the priority of the present application is valid.

In particular, compounds are disclosed in pages 52 (the fourth compound of the page), 53 (the fourth compound), having R3=H, and in page 54 (the last compound) having R3=NR13R14 in a cycle (differing from the present compounds in that there is a oxo group in the cycle).

Article 54(2) EPC

5. D3 is not relevant.

It discloses different compounds for treating Alzheimer's disease.

Inventive step

6.1 The subject matter of the present application, as far as novel and as far as its priority is not valid, lacks an inventive step in view of D1.

D1, as far as the priority of the present application is not valid, can be used as a starting point for the discussion of inventive step of those compounds for which the priority of the application is not valid, being published before the effective date (filing date) of the application.

D1 discloses compounds having a formula falling under the presently claimed formula, as being inhibitors of beta secretase, useful in therapy for treating Alzheimer's disease and other disorders characterised by elevated amyloid levels: see claim 1 and in particular the compounds E245, E246, E250, E288, E337, E338-E343, E345-E348, E431, E439, E440, E442-E445, E448, E449, E472, E479, E279, mentioned above in paragraph 4.1. The present application (as far as its priority is not valid) differs from the compounds of D1 in that Q2,Q3 are halogen instead of hydrogen, or in that Rb is the group (3) of the list of claim 1, or R78 is group (c) of claim 1 or R4-R7 together form the group (b) of claim 1 or finally R17 is group (g) of claim 1.

The problem to be solved by the present application is to provide an alternative secretase inhibitor for treating Alzheimer.

It would be obvious for the man skilled in the art to perform the small modifications of the compounds of D1 in order to obtain the presently claimed compounds of formula (I) for which the priority is not valid, and expect from them an activity as secretasis inhibitors for treating Alzheimer's disease.

The subject matter of present claims 1-19 is therefore not inventive in view of D1, as far as the priority of the present application is not valid.

However, as far as the priority of the application is valid, D1 is too late for being used for discussing inventive step.

6.2 The subject matter of present claims 1-19, as far as the priority of the present application is valid, and as far as novel, seems to be inventive.

The closest prior art is D3 relating to the same use of similar compounds.

D3 discloses similar compounds having Ra=dimethylbutyl carbamoyl instead of a alkyl amino group, Q1= OH pentyl instead of OH.

They are used as inhibitors of Asp2 (secretase) for treating Alzheimer's disorder.

The present application differs from D2 in that the compounds claimed for the same use, and having the same activity on secretase, have Q1=OH and not OH pentyl- and Ra=alkyl amino instead of a carbamoyl moiety.

The problem to be solved by the present application is to provide an alternative secretase inhibitor for treating Alzheimer.

It would not be obvious for the man skilled in the art to modify the compounds of D3 in order to obtain the presently claimed compounds and expect from them an activity as secretasis inhibitors for treating Alzheimer's disease.

6.3 D2 discloses different compounds for treating Alzheimer's disease. Being prior art under Article 54(3) EPC, it is not relevant, as far as the priority of the present application is valid.

In particular, compounds are disclosed in pages 52 (the fourth compound of the page), 53

(the fourth compound), having R3=H, and in page 54 (the last compound) having R3=NR13R14 in a cycle (differing from the present compounds in that there is a oxo group in the cycle).

Conclusion

7. The applicant is requested to restrict the claims in order to overcome the novelty and inventive step objections in view of D1, without contravening Article 123(2) EPC.

A basis in the original application for the amendments performed should be provided.

Care should be taken not to define subformulas of the presently claimed formula (I), by deleting groups or substituents of formula (I), for which no basis under Article 123(2) EPC exists in the original application.

In this respect, the attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 123(2) EPC) and that refusal of the application is to be anticipated if the requirements of Article 123(2) EPC are not met.

When filing new claims, the applicant is required to take notice of the following: in order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

Arguments in favour of inventive step should be provided.

The description must be adapted to the amended claims.

Camilla Bonzano